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(54) Bis-urethanes and bis-carboxylic esters of 2-bromo-2-nitro-propane-1,3-diol and their use as biocides

(57) Biocidal compounds having the formula R.Y.CO.O.CH_2-C(BR)(NO_2)-CH_2.O.CO.Y.R wherein each Y is either a direct link or an —NH— group and R is certain optionally substituted hydrocarbon radicals, the preparation of these compounds and their use for the protection of materials from microbial attack.

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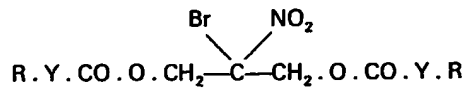
SPECIFICATION

Biocides

This invention relates to biocides and more particularly to biocides derived from 2-bromo-2-nitropropane-1,3-diol.

The compound 2-bromo-2-nitropropane-1,3-diol is known to have antibacterial and antifungal activity, for example, as disclosed in United Kingdom Patent Specification No. 1,057,131. It has now been found that certain derivatives of 2-bromo-2-nitropropane-1,3-diol also have biocidal activity and have the advantage over the diol itself of greater stability, lower toxicity and also that it is possible specifically to tailor the properties of the derivatives according to their intended end use.

According to the present invention there are provided compounds having the general formula:



wherein each Y is either a direct link or an —NH— group and R is an unsubstituted straight chain or branched alkyl radical containing from 2 to 18 carbon atoms, a substituted straight chain or branched alkyl radical containing from 1 to 18 carbon atoms, or an optionally substituted alkenyl, cycloalkyl, aralkyl, alkaryl or aryl radical.

Examples of substituents which may be present in the radical R are hydroxyl, chloro, bromo, cyano, lower alkoxy, nitro and acyloxy. By "lower alkoxy" we mean alkoxy radicals containing from 1 to 4 carbon atoms. Specific examples of the radicals represented by R are ethyl, *n*-propyl, isopropyl, *n*-butyl, hexyl, octyl, dodecyl, stearyl, allyl, cyclohexyl, benzyl, 2-phenylethyl, phenyl, *o*-, *m*- and *p*-tolyl, *o*-, *m*- and *p*-chlorophenyl, *o*-, *m*- and *p*-bromophenyl, *o*-, *m*- and *p*-nitrophenyl and α- and β-naphthyl.

According to a further feature of the invention there is provided a process for the manufacture of the compounds as hereinbefore defined wherein each Y is an —NH— group which comprises reacting together 1 molecular proportion of 2-bromo-2-nitropropane-1,3-diol and approximately 2 molecular proportions of a monoisocyanate R . NCO wherein R has the meaning defined above.

The reaction is carried out by methods well known in the polyurethane art, and it is preferred to use a slight excess of the monoisocyanate over the diol so that there are no free hydroxyl groups in the product.

Examples of suitable monoisocyanates R . NCO are ethyl isocyanate, *n*-propylisocyanate, isopropyl isocyanate, dodecyl isocyanate, stearyl isocyanate, allyl isocyanate, cyclohexylisocyanate, benzyl isocyanate, phenyl isocyanate, *o*-, *m*- and *p*-tolylisocyanate and α-naphthylisocyanate. Mixtures of isocyanates may be used, in which case the groups R in the compounds of the invention may not be the same.

The reaction between the 2-bromo-2-nitropropane-1,3-diol is preferably carried out in a solvent which is inert to isocyanate groups. Suitable solvents are essentially anhydrous esters, ketones, hydrocarbons, halogenated hydrocarbons and amides, for example, urethane grades of ethyl acetate, butyl acetate, methyl ethyl ketone, methyl isobutyl ketone, 4-methoxy-4-methylpentan-2-one, toluene, xylene, trichloroethylene, dimethylformamide and dimethlyacetamide.

The reaction may be carried out at room temperature or at a moderately elevated temperature, for example, up to 90°C or even higher.

The reaction between the 2-bromo-2-nitropropane-1,3-diol and the monoisocyanate is preferably carried out in the presence of a catalyst of the kind which accelerates the reaction between an isocyanate group and a hydroxyl group. Examples of such catalysts are organic and inorganic basic compounds, and soluble organic compounds of metals, for example, of transition metals, such as iron and manganese acetylacetonate, and of tin and antimony, for example, stannous octoate and dibutyl tin dilaurate, and compounds of lead such as lead acetate, basic lead acetate and lead 2-ethylhexoate. As basic organic catalysts tertiary amines are suitable, particularly 4-dimethylaminopyridine, triethylenediamine, dimethylbenzylamine and dimethylcyclohexylamine. Mixtures of catalysts may be used, especially mixtures of metal-containing and amine catalysts.

The reaction product of the 2-bromo-2-nitropropane-1,3-diol and the monoisocyanate R . NCO may be isolated from the reaction mixture by conventional means, i.e. by filtration if the product separates out after reaction is complete, or by removal of the solvent, e.g. by evaporation or preferably by distillation, if desired under reduced pressure, and isolation of the residual product, which may be further purified by washing with a liquid in which it has little or no solubility, or by crystallisation from a suitable solvent.

According to a yet further feature of the invention there is provided a process for the manufacture of the compounds as hereinbefore defined wherein each Y is a direct link which comprises esterifying 1 molecular proportion of 2-bromo-2-nitropropane-1,3-diol with approximately 2 molecular proportions of a monocarboxylic acid R . COOH wherein R has the meaning defined above.

Examples of suitable monocarboxylic acids are monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid, glycollic acid, propionic acid, *n*-butyric acid, *n*-hexanoic

acid, *n*-octanoic acid, decanoic acid dodecanoic acid, hexadecanoic acid, stearic acid, cyclohexane carboxylic acid, phenylacetic acid, benzoic acid, *o*-, *m*- and *p*-toluic acid and *α*-naphthoic acid.

The reaction is carried out by known methods, e.g. the 2-bromo-2-nitropropane-1,3-diol and the monocarboxylic acid are heated together in the presence of a catalytic amount of a strong acid such as sulphuric acid or *p*-toluenesulphonic acid under conditions such that the water which is formed in the reaction distils out from the reaction mixture. If desired the reaction may be carried out in a solvent for the diol and the monocarboxylic acid, the water produced in the reaction being distilled out azeotropically with a part of the solvent. The ester which is formed is isolated from the reaction mixture by known methods, e.g. methods similar to those indicated above for the corresponding urethanes.

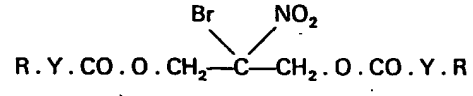
An alternative process for the manufacture of the compounds of the invention in which Y is a direct link comprises transesterifying a lower alkyl ester of a carboxylic acid R . COOH, wherein R has the meaning defined above, with 2-bromo-2-nitropropane-1,3-diol.

The transesterification reaction is preferably carried out under conditions such that the lower alkanol which is also formed distils out of the reaction mixture.

By "lower alkyl" we mean alkyl radicals containing from 1 to 4 carbon atoms. Methyl esters are preferred. The reaction is preferably catalysed by a strong acid as indicated previously.

The compounds of the invention may also be obtained by reaction of 2-bromo-2-nitropropane-1,3-diol with an acid halide or anhydride of a carboxylic acid R . COOH, wherein R has the meaning defined above, or with a lactone such as *γ*-butyrolactone, or a hydroxyacid such as *p*-hydroxybenzoic acid, the reactions being carried out by known methods.

The compounds of the present invention are valuable biocides, and according to a still further feature of the invention there is provided a method for protecting a medium which is susceptible to attack by micro-organisms against such attack, and controlling or preventing the proliferation of micro-organisms in a medium already infected thereby, which comprises adding to the said medium a biocidal amount of a compound having the general formula:



wherein R and Y have the meanings defined above.

In the above definition, preventing the proliferation of micro-organisms means that the micro-organisms are not allowed to multiply further, the number of micro-organisms not necessarily being substantially altered. Controlling the proliferation of micro-organisms means that the rate of multiplication of the micro-organisms is either reduced or rendered negative (i.e. a reduction in numbers, including the case of complete eradication).

The biocides are particularly useful in the treatment of aqueous media, for example, industrial cooling waters, the water systems of paper mills, aqueous oil emulsions such as metal-working fluids, water-based paints (i.e. emulsion paints) and water-based adhesives, but they also find application as paint film fungicides and in the prevention of fungal and/or bacterial attack on wood and leather, and are also active against algae.

The amount of biocide which is used will depend upon the medium which is being treated but for aqueous media an amount from 1 to 1,000 parts per million by weight, based on the weight of the medium, is generally effective.

When used as a paint film fungicide the biocidal compound will generally be used in an amount to provide a concentration in the paint, before its application to a substrate, of from 500 to 10,000 parts per million by weight.

The invention is illustrated but not limited by the following Examples, in which parts and percentages are by weight.

EXAMPLE 1

Preparation of the reaction product from 2-bromo-2-nitropropane-1,3-diol and isopropyl isocyanate.

11.7 Parts of 2-bromo-2-nitropropane-1,3-diol are suspended in 86 parts of dry toluene. 0.5 Part of dibutyl tin dilaurate and 0.4 part of triethylamine dissolved in 5 parts of toluene are added to the suspension and 10 parts of isopropyl isocyanate are added portionwise, with constant stirring of the reaction mixture. A short time after addition of the isocyanate is complete, the temperature of the reaction mixture rose from 22° to 30°C. The mixture is stirred for a further 10 minutes to ensure that the exotherm is complete. The temperature of the reaction mixture is then raised to 60°C and held at this level for 90 minutes, after which the mixture is allowed to cool to room temperature. The resulting clear solution is filtered to remove slight traces of insoluble material and is then evaporated to dryness, yielding a viscous liquid which eventually crystallised to give a yellow-brown solid. Recrystallisation of the solid from ethyl acetate/cyclohexane gives a product having m.p. 100—102°C. Yield 7.5 parts. The infra-red spectrum shows a strong carbonyl band at 1700 cm^{-1} and a sharp NH band at 3290 cm^{-1}.

Elementary analysis: C, 36.0; H, 5.8; N, 11.3; Br, 22.5%. $C_{11}H_{20}BrN_3O_6$ requires C, 35.6; H, 5.4; N, 11.3; Br, 21.6%.

EXAMPLE 2

Testing of the product of Example 1 for antibacterial and antifungal activity.

The product obtained as described in Example 1 is incorporated into molten nutrient agar and malt agar to give final concentrations in each case of 100 parts per million (ppm) by weight.

The biocide-containing agar is poured into Petri dishes and allowed to solidify. Plates containing the biocide are poured in triplicate.

A microtiter AM 80 Automatic Inoculator is used for inoculating the agar plates. The nutrient agar plates are inoculated with the bacteria *Pseudomonas aeruginosa (Ps. aerug), Escherichia coli (E. coli)* and *Staphylococcus aureus (S. aureus)*, and the malt agar plates are inoculated with the fungi *Pullularia pullulans (P. pullulans), Aspergillus niger (Asp. nig.), Cladosporium sphaerospermum (Clad. Sphaer), Alternaria tenuis (Alt. ten.)* and *Chaetomium globosum (Chaet. glob).*

The nutrient agar plates are incubated at 37°C for 24 hours and the malt agar plates are incubated at 25°C for 48 hours, after which the plates are examined for the presence or absence of microbial growth.

Results are as follows:

Biocide (at 100 ppm)	Growth of							
	Ps aerug	*E. coli*	*S. aureus*	*P. pullulans*	*Asp. nig.*	*Clad. spaer*	*Alt. ten.*	*Chaet glob*
Compound of Example 1	+	+	+	–	–	–	–	–

In the above table, + indicates microbial growth and – indicates absence of microbial growth.

These results indicate that the compound of Example 1 has high antifungal activity.

EXAMPLE 3

Preparation of the bis(chloroacetate) of 2-bromo-2-nitropropane-1,3-diol

(a) 11.7 Parts of 2-bromo-2-nitropropane-1,3-diol, 10.96 parts of monochloroacetic acid and 0.5 part of *p*-toluenesulphonic acid are suspended in 129 parts of dry toluene. The mixture is heated under reflux, the water which is formed in the esterification reaction being collected in a Dean and Stark apparatus. When the evolution of water ceases the solution is cooled, filtered and the toluene is removed on a rotary evaporator to give the product as a dark oil. The yield is 19.3 parts. The infra-red spectrum shows a strong carbonyl absorption at 1750 cm^{-1}.

If in the above preparation the monochloroacetic acid is replaced by an equimolar amount of (b) dichloroacetic acid or (c) trichloroacetic acid or (d) monobromoacetic acid or (e) glycollic acid, then similar products are obtained. Details of physical form of products, yields and infra-red spectral data are as follows:

(b) Oil. Yield 23.5 parts. Strong carbonyl band at 1770 cm^{-1}.

(c) Viscous oil. Yield 15.7 parts. Carbonyl band at 1790 cm^{-1}.

(d) Oil. Yield 11.45 parts. Strong carbonyl band at 1745 cm^{-1}.

(e) Oil. Yield 10.52 parts. Strong carbonyl band at 1740 cm^{-1}.

Strong broad band at 3350 cm^{-1}. Elementary analysis: Found C, 26.6; H, 3.5; N, 3.5;Br, 25.5%. $C_7H_{10}BrNO_8$ requires C, 26.6; H, 3.2; N, 4.4; Br, 25.3%.

EXAMPLE 4

The procedure described in Example 1 is repeated except that the 10 parts of isopropyl isocyanate are replaced by 14 parts of phenyl isocyanate. There are obtained 12.97 parts of product, m.p. 123—124°C. The infra-red spectrum showed a strong carbonyl absorption at 1735 cm^{-1} and NH absorption at 3400 cm^{-1}.

EXAMPLE 5

Testing of the product of Examples 3 and 4 for antibacterial and antifungal activity.

The tests are carried out exactly as described in Example 2. Results are as follows:—

Biocide (at 100 ppm)	Growth of							
	P aerug	*E coli*	*S aureus*	*P pullulans*	*Asp. nig.*	*Clad sphaer*	*Alt ten.*	*Chaet glob.*
Example 3(a)	–	–	–	+	+	+	NT	+
,, 3(b)	–	–	–	+	+	+	NT	+
,, 3(c)	–	–	–	+	+	+	NT	+
,, 3(d)	–	–	–	+	+	+	NT	+
,, 3(e)	–	–	–	+	+	+	NT	+
,, 4	+	+	+	–	–	–	+	+

In the above table, + indicates microbial growth, — indicates absence of microbial growth and NT indicates that the compound was not tested against that micro-organism.

These results indicate that the esters (Example 3(a) to 3(e) inclusive) are active against all the bacteria and that the bisurethanes (Example 4) is active against certain of the fungi.

EXAMPLE 6

Testing of the products of Examples 3(a), 3(b), 3(c) and 3(d) for antibacterial activity in metal-working fluid.

A 5% oil-in-water emulsion is prepared by adding Prosol 44 (Trade Mark) (Mobil) to tap water, and dispensed in 100 ml volumes in 250 ml sterile conical flasks. 1% solutions of the polymers under test are prepared in dimethylformamide and added to the emulsions to give final concentrations of 100 and 200 ppm active ingredient. The control consists of an emulsion containing the equivalent volume of dimethylformamide required to make up the volume of emulsion to 200 ml if biocide had been present.

The 100 ml volumes of emulsions are inoculated with 0.5 ml of a 24 hour broth culture of *Ps. aeruginosa* once weekly for 2 weeks.

The inoculated emulsions are incubated at 30°C in a rotary shaker (80 revolutions per minute) and each week for 2 weeks at 24 hours and 3 days after inoculation 1 ml samples are removed and surviving bacteria are determined in nutrient agar by the standard decimal dilution procedure.

Results are as follows:

Treatment		Survivors (cells/ml emulsion) in			
		Week 1		Week 2	
		Day 1	Day 3	Day 1	Day 3
Example 3(a)	200 ppm	<10	<10	<10	2.0×10^{1}
	100 ppm	<10	<10	$>3.0\times10^{5}$	5.0×10^{4}
Example 3(b)	200 ppm	<10	<10	<10	<10
	100 ppm	<10	<10	$>3.0\times10^{5}$	$>3.0\times10^{5}$
Example 3(c)	200 ppm	<10	<10	1.0×10^{1}	1.0×10^{1}
	100 ppm	<10	<10	<10	<10
Example 3(e)	200 ppm	<10	<10	<10	<10
	100 ppm	<10	<10	$>3.0\times10^{5}$	$>3.0\times10^{5}$
Control		8.4×10^{6}	2.6×10^{6}	$>3.0\times10^{7}$	$>3.0\times10^{7}$

These results indicate that the compounds tested have high activity as metal-working fluid biocides.

EXAMPLE 7

Testing of the products of Examples 3(b), 3(c) and 3(e) for activity as in-can paint preservatives.

1% solutions of the biocides in dimethylformamide (DMF) are added to 50 g quantities of a styrene-acrylic emulsion paint to give final biocide concentrations of 100 and 200 ppm. The controls consist of paints minus biocide but containing a DMF level equivalent to that required to provide 200 ppm of biocide.

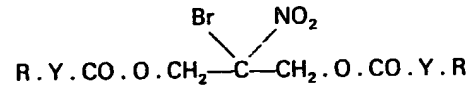
Once weekly for two successive weeks the biocide-containing paints are inoculated with 1 ml of a mixture of *Ps. aeruginosa, E. coli* and *Enterobacter cloacae*. The inoculated paints are incubated at 30°C and each week 1 and 3 days after inoculation surviving bacteria are determined in the samples by the standard decimal dilution procedure.

Treatment		Survivors (cells/g paint) in			
		Week 1		Week 2	
		Day 1	Day 3	Day 1	Day 3
Example 3(b)	200 ppm	<10	<10	2.0×10^3	<10
	100 ppm	2.0×10^4	1.5×10^4	6.0×10^5	3.0×10^5
Example 3(c)	200 ppm	<10	<10	<10	<10
	100 ppm	<10	<10	1.0×10^3	<10
Example 3(e)	200 ppm	<10	<10	1.2×10^3	<10
	100 ppm	4.0×10^4	3.0×10^4	3.0×10^5	$>3.0\times10^5$
Control		2.0×10^7	8.0×10^6	3.0×10^7	$>3.0\times10^7$

These results show that the compounds tested have high activity as in-can paint preservatives.

CLAIMS

1. Compounds having the general formula:



wherein each Y is either a direct link or an —NH— group and R is an unsubstituted straight chain or branched alkyl radical containing from 2 to 18 carbon atoms, a substituted straight chain or branched alkyl radical containing from 1 to 18 carbon atoms, or an optionally substituted alkenyl, cycloalkyl, aralkyl, alkaryl or aryl radical.

2. Compounds substantially as hereinbefore described in any one of the foregoing Examples 1, 3 and 4.

3. A process for the manufacture of the compounds claimed in claim 1 wherein each Y is an —NH— group which comprises reacting together 1 molecular proportion of 2-bromo-2-nitropropane-1,3-diol and approximately 2 molecular proportions of a monoisocyanate R . NCO wherein R has the meaning stated in claim 1.

4. A process as claimed in claim 3 wherein the monoisocyanate is used in slight molar excess over the diol.

5. A process as claimed in claim 3 substantially as hereinbefore described in the foregoing Example 1 or Example 4.

6. A process for the manufacture of the compounds claimed in claim 1 wherein each Y is a direct link which comprises esterifying 1 molecular proportion of 2-bromo-2-nitropropane-1,3-diol with approximately 2 molecular proportions of a monocarboxylic acid R . COOH wherein R has the meaning stated in claim 1.

7. A process as claimed in claim 6 substantially as hereinbefore described in the foregoing Example 3.

8. A process for the manufacture of the compounds claimed in claim 1 wherein each Y is a direct link which comprises transesterifying a lower alkyl ester of a carboxylic acid R . COOH, wherein R has the meaning stated in claim 1, with 2-bromo-2-nitropropane-1,3-diol.

9. A process for the manufacture of the compounds claimed in claim 1 wherein each Y is a direct link which comprises reacting 2-bromo-2-nitropropane-1,3-diol with an acid halide or anhydride stated in claim 1, or with a lactone or a hydroxyacid.

10. Compounds as claimed in claim 1, obtained by a process as claimed in any one of claims 3 to 9.

11. A method for protecting a medium which is susceptible to attack by micro-organisms against such attack, and controlling or preventing the proliferation of micro-organisms in a medium already infected thereby, which comprises adding to the said medium a biocidal amount of a compound as claimed in claim 1.

12. A method as claimed in claim 11 wherein the medium is an aqueous medium and the compound is used in an amount from 1 to 1000 parts per million by weight based on the weight of the aqueous medium.

13. A method as claimed in claim 11 wherein the medium is a paint film and the compound is used in an amount from 500 to 10,000 parts per million by weight based on the weight of paint before its application to a substrate.

14. A method as claimed in claim 1 substantially as hereinbefore described in any one of the foregoing Examples 2 and 5 to 7.

15. Media which are susceptible to attack by micro-organisms, protected against such attack by a method as claimed in any one of claims 11 to 14.

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